CASE REPORT

Insulin allergy

Peter J Raubenheimer, Naomi S Levitt

Allergic reactions to insulin are distinctly unusual with recombinant human insulin. When they occur, however, they can be associated with severe symptoms, making it difficult to treat patients who are insulin-dependent. Whether the increased use of insulin analogues will further reduce the allergic manifestations first seen with animal insulin remains uncertain.

Case history

A 57-year-old man with type 2 diabetes presented to the emergency department of Groote Schuur Hospital, Cape Town, complaining of an itchy rash which he related to his insulin injection. He had had diabetes for about 10 years, and had been switched to insulin (Actraphane twice daily) 1 year previously, because of poor control with an HbA_{1c} of 9.5% (normal range < 5.8%) on maximal doses of oral agents. There had been symptomatic improvement after starting the insulin, although best HbA_{1c} was still poor at 8.8%. Insulin was well tolerated until 1 month before presentation, when he noted a very itchy rash on his trunk, neck and arms 1 - 2 hours after injecting. This persisted for a few hours, improved, and then recurred after his next injection. The rash had become progressively more severe over the last month. There was no allergic history otherwise.

About 30 minutes after 10 units of short-acting human insulin (Humulin R) was administered subcutaneously as a test dose the patient developed a generalised and severe urticarial reaction. There was no nasal irritation, peri-orbital oedema or swelling of the tongue or lips. There was no wheeze or shortness of breath. His insulin treatment was stopped, maximal dosages of oral agents were recommenced and strict dietary habits maintained. However, glycaemic control deteriorated (HbA_{1c} 12.7%) and symptoms of hyperglycaemia developed again. He was therefore admitted for insulin desensitisation.

Skin testing was performed intradermally with dilutions of human short-acting insulin (Actrapid) and confirmed allergy to the insulin molecule itself, with a wheal and flare reaction developing at 0.001 units of insulin. The patient had positive immunoglobulin E (IgE) antibodies to porcine (1.77 kU/l) and human insulin (1.29 kU/l).

Peter Raubenheimer specialised in internal medicine and endocrinology at Groote Schuur Hospital, Cape Town, and is currently in Edinburgh doing a PhD on the role of glucocorticoid metabolism in obesity. Dinky Levitt is a professor in the Department of Medicine, University of Cape Town, where she works in the Division of Diabetic Medicine and Endocrinology.

Desensitisation was carried out over 4 days with subcutaneous injections of increasing concentrations of human insulin as per set protocol, after which insulin was much better tolerated. Occasional allergic reactions still occurred but were well controlled by antihistamines as needed.

Discussion

Soon after the introduction of animal insulin for the treatment of diabetes in 1922, immunological complications of insulin became evident. Insulin allergy was particularly common, with local symptoms occurring in up to 50% of patients treated with unchromatographed insulin.[1] However, early insulins were very impure, and were either single species or mixtures of bovine and porcine insulin, and contained several islet-cell peptides, which are all immunogenic. With the introduction of highly purified porcine insulin and recombinant human insulin, allergic reactions were far less common, occurring in about 3% and less than 1% of cases respectively.[2]

By far the most common type of insulin allergy is a type I hypersensitivity reaction mediated by IgE, which can result in local or generalised reactions. This biphasic reaction has a typical time course characterised by an immediate wheal and flare, followed about 6 hours later by a repeat reaction that may persist for days. Interestingly, allergy is usually to the insulin molecule itself. IgE antibodies to insulin are invariably present and are usually found in high titre in patients with generalised allergy,[3] but may develop in people with no manifestations of allergy to insulin, and are therefore only helpful in excluding the diagnosis. Protamine (a complexing agent to prolong the duration of action of insulin) and zinc (stabiliser) have also been implicated in insulin allergy. IgE antibody directed to protamine is common in patients treated with protamine-containing insulin, but the prevalence of clinically evident protamine allergy is low. It is important to note that a serious generalised reaction to protamine, given to neutralise heparin anticoagulation following cardiac surgery, has been described in patients with antibodies to protamine.[4]

Treatment

Local reactions to insulin tend to be self-limited, with improvement seen within 1 - 2 months with continued insulin use. However, if reactions persist for more than 2 weeks, the following approach is recommended.

1. Rule out poor injection technique, impurities in cleansing alcohol, and infection.

2. Switch to human insulin, if the patient is still on animal insulin. Consider the insulin analogues lispro, aspart or glargine, which are less immunogenic.[5-9]

3. If no improvement: (*i*) reduce the dose given at a single site by 50%, by using two injection sites; (*ii*) consider zinc-free insulin (available from manufacturers); and (*iii*) use local steroids in low doses.

4. Consider using long-acting antihistamines.

With such a technique 90% of patients will improve within 2 months,[10] and over half of the remainder will improve spontaneously over 6 - 12 months. If there is deterioration in the severity of the local reaction it may herald a generalised reaction and management as for such a reaction is appropriate; it would be prudent to issue an adrenalin delivery device, e.g. Epipen (Merck) to manage symptoms of anaphylaxis.

Features of generalised allergy to insulin range in severity and include urticaria, angio-oedema, pruritus, paraesthesiae, pallor, flushing, palpitations, bronchospasm, respiratory distress due to laryngeal oedema and frank circulatory collapse. No case of death has been reported.

If evaluated within 24 - 48 hours of a mild, generalised allergic reaction, consider continuing the insulin, hospitalising the patient and reducing the dose to 1/3 or 1/4 of the original and then gradually increasing the dose over several days.[11] If available, it would be prudent to change to insulin analogues. If insulin therapy has been interrupted for more than 48 hours or if previous allergic reactions have been particularly severe, then skin testing and possible desensitisation are indicated. For such a procedure, the patient is hospitalised and advice from an experienced diabetologist and allergologist is recommended. In the presence of significant hyperglycaemia and/or a deteriorating metabolic condition desensitisation should be started immediately, otherwise it can be scheduled electively. In a patient with keto-acidosis, intravenous insulin is generally well tolerated and can be given until metabolically stable before attempting desensitisation. Fortunately desensitisation is effective, with one study reporting a 94% success rate.

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